REMARKS

Claims 2-37 are pending in the present application; claims 2, 3, and 17-37 are under consideration, as claims 4-16 were removed from consideration by the Examiner after restriction. Claims 2-5, 12, 13, 15-17 and 24-27 have been amended. Claims 2-4 and 24-37 have been amended to refer to specific nm23 polypeptide sequences, i.e., a coding region of SEQ ID NOs:3 and/or 5; support for these amendments can be found, e.g., at page 10, lines 11-15; page 13, line 6 to page 14, line 3; and page 14, lines 9-12. Claim 5 has been amended to correct typographical errors affecting antecedent basis and to refer to specific Rad and nm 23 polypeptide sequences, i.e., a coding region of SEQ ID NOs:1, 3, and 5; support for these amendments can be found, e.g., at page 13, line 6 to page 14, line 3. Claims 12, 13, 15, and 16 have been amended to correct typographical errors affecting antecedent basis, replacing "the" with "an." Claim 17 has been amended to refer to a polypeptide that "comprises a biologically active fragment of a coding region of SEQ ID NO:3 or 5; support for these amendments, including the definition of "biological activity," can be found, e.g., at page 10, lines 11-15; and page 13, line 6 to page 14, line 3. Claims 17, 24, and 32-37 were additionally amended to depend from claim 2 rather than claim 3.

Applicants submit herewith an initial Sequence Listing as required under 37 CFR §1.823(a), a Sequence Listing in computer readable form as required by 37 CFR §1.824, and a statement under 37 CFR §1.821(f). The specification has been amended to insert the paper copy of the sequence listing, and to insert references to the sequence listing as appropriate. The undersigned hereby declares that no new matter has been added.

Objection to the Specification

At page 3 of the Office Action, the Examiner objected to the incorporation by reference at page 13, line 6 – page 14, line 3 as improper.

Applicants note that incorporation by reference is an accepted procedure, see MPEP §2163.07(b), which recites, in relevant part:

> Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter.

Applicants enclose herewith an amendment and sequence listing, inserting the information previously incorporated by reference. SEQ ID NO:1, the Rad polypeptide sequence, is shown in Figure 1 of Zhu et al., 1995, JBC 270:4805-4812, at page 4807. SEQ ID NOs:2 (nm23H1 nucleotide) and 3 (nm23H1 polypeptide)) are described in Figure 4 of Steeg et al., 1988, J. Natl. Cancer Inst. 80: 200-204. SEQ ID NOs: 4 (nm23H2 nucleotide) and 5 (nm23H2 polypeptide)) are described in Figure 1 of Stahl et al., 1991, Cancer Res 51:445-449.

Applicants enclose a declaration, executed by the undersigned practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the present application. See MPEP §608.01(p)(I)(A)(2), and In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). Applicants submit that, under MPEP §2163.07(b), this amendment does not introduce any new matter and removes the incorporation by reference objected to by the Examiner. Thus, Applicants request withdrawal of the objection to the specification.

Claim Rejections

At pages 3-5 of the office action, the Examiner rejected claims 3 and 17-37 as allegedly failing to comply with the written description requirement of 35 USC § 112, ¶1. In part, the rejection reads as follows:

> The specification, claims and art do not indicate what distinguishing characteristics are concisely shared by members of the genus comprising an nm23, nm23H1 or nm23H2 polypeptide, a fragment of nm23 polypeptide, or a homolog of nm23 polypeptide that, when administered to a call, modulates the activity of Rad in that cell. No sequences were provided in the instant disclosure for any members of this broad genus comprising nm23, nm23H1 or nm23H2

> polypeptides, or fragments or homologs of nm23 polypeptide. The specification does not place any limit on the number of amino acid substitutions, deletions, insertions or additions that may be made to the members of this broad genus. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number [of] structural differences between genus members is permitted. Concise structural features that could distinguish compounds in the genus are missing from the disclosure and the art.

The specification, at page 13, line 6 to page 14, line 4, defined the nm23H1 and nm23H2 polypeptides as those set forth in the Steeg et al., 1988, and Stahl et al., 1991, references, respectively. Applicants have amended the specification to insert a sequence listing including those sequences, as described above. In addition, applicants have amended independent claim 2 to recite "modulating the level of nm23 in the cell by administering to the cell a polypeptide that comprises at least 60% sequence identity with a coding region of SEQ ID NO:3 or 5, wherein the polypeptide has at least one nm23 biological activity selected from the group consisting of (1) binding to Rad; (2) promoting a Rad activity; (3) nucleotide diphosphokinase activity; and (4) inhibiting the binding of Rad and nm23." Support for this amendment can be found at page 10, lines 11-15, and page 13, line 6 to page 14, line 20. This amendment provides a specific structure, by providing the sequence identification numbers of nm23H1 and nm23H2 polypeptides. The number of variants is limited, both by the requirement that the polypeptide have at least 60% sequence identity with a coding region of one of the identified sequences, and that the polypeptide must have at least one of the recited nm23 biological activities. One of skill in the art, given the teachings of the specification as filed, would readily understand that the inventors had possession of the claimed invention at the time the application was filed.

Claims 2, 3, and 17-37 were rejected at pages 5-8 as lacking sufficiently enabling disclosure in the specification for modulating Rad activity *in vivo*. The Examiner cited a number of references to "illustrate that the delivery of polypeptides to a target cell in vitro or in vivo is energy dependent and requires the presence of specific proteins that serve as receptors and or channels." Applicants respectfully submit that this statement is scientifically inaccurate, as there are a number of methods known in the art that do not require the presence of specific receptors or

channels. While some proteins no doubt may be delivered in such a fashion, one of skill in the relevant art at the time of filing would have been well aware of a number of other methods for delivering polypeptides to a cell in vivo.

As one example, liposomal delivery systems are believed to involve the fusion of hydrophobic liposomes into hydrophobic cell membranes, depositing the contents of the liposome on the other side – the interior of the cell. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. As noted in MPEP § 2164.08,

> ...not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

See also *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Furthermore, per MPEP 2164.01(c), "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." One skilled in the art, based on knowledge of other protein compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation; this is sufficient to satisfy 35 U.S.C. § 112, ¶1.

Per MPEP §2164.05, "Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application."

Liposomal delivery systems were known and in development at the time of filing, see, e.g., Chonn and Cullis, "Recent Advances in Liposome Drug Delivery Systems," Current Opinion in Biotechnology 6:698-708 (1995); Weiner, "Liposomes for Protein Delivery: Selecting Manufacture and Development Processes," Immunomethods 4(3)201-9 (1994); and

Gregoriadis, "Engineering Liposomes for Drug Delivery: Progress and Problems," Trends Biotechnol. 13(12):527-37 (1995).

These publications, all of which were published at least two years before the relevant date, demonstrate that at that time of filing, systems for intracellular protein delivery were known in the art. Copies of all of these references are submitted herewith for the Examiner's consideration.

Chonn and Cullis, 1995, disclose that "liposomes can facilitate the intracellular delivery of drugs by fusing with the target cell." (p. 700) The inclusion of other species in the lipid mixture of the liposomes was known in the art to enhance fusion events, see, e.g., Lee et al., J Biol Chem. 271(13):7249-52 (1996), which discloses methods for delivery of macromolecules into the cytosolic space of macrophages from liposomes that contain listeriolysin O (LLO). Gregoriadis, 1995, includes a list of liposome-delivered drug products that were in clinical trials at that time or under development.

An approach similar to the claimed methods was used successfully in Mizguchi et al., Cancer Lett. 100:63-69 (1996), which describes the use of fusogenic liposomes to deliver a protein, fragment A of diphtheria toxin (DTA), to tumor cells both *in vivo* and *in vitro*. DTA is a potent inhibitor of protein synthesis which must be delivered to the cytoplasm of tumor cells. The fusogenic liposomes used in Mizguchi et al. were based on Sendai virus, but did not show any severe side effects when injected directly into the abdominal cavity of mice. The liposomes were demonstrated to fuse with a wide variety of cultured cells *in vitro*. The use of the liposomal systems described in Mizguchi et al. led to suppression of tumor growth in a dose-dependent manner.

Per MPEP § 2164, to comply with 35 U.S.C. § 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) (an invention directed to a general system to improve the cleaning process for semiconductor wafers was enabled by a disclosure showing improvements in the overall system). As the description of the invention itself is sufficient to

permit those skilled in the art to make and use the invention, detailed procedures for making and using the invention are not necessary.

Applicants submit that, given the guidance supplied by the specification, and the level of knowledge in the art regarding protein delivery systems, one of skill in the art would have been able to make and use the invention commensurate with the scope of claims without undue experimentation.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10276-017002.

Respectfully submitted,

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